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Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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1. Hatfield, M. A.; Simpson, R. A., and Jackson, R. L.: J. Pediat. 44: 32-45 (Jan.) 1954. 2. Frost, L. N., and Jackson, R. L.: J. Pediat. 39: 585-592 (Nov.) 1951. 3. Henricksen, W. E.: GP 8: 51-56 (Oct.) 1953. 4. Litchfield, H. R.: Arch. Pediat. 61: 617 (Dec.) 1944.

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Selection of Infants With Congenital Heart Disease for Surgery

WILLIS J. POTTS, M.D.*, ALEXANDER S. NADAS, M.D.†
AND BERNARD J. WALSH, M.D.‡

Dr. Walsh:

One of the interesting aspects of our recent advances in the diagnosis and treatment of congenital heart and vascular defects has been the pressure we put on ourselves, and the pressures that are put on us by our colleagues and by parents to do something at a younger and younger age, even under the age of 1 year, for children who have significant cardiac defects. So we thought we might start off this conference by hearing from our panelists as to some of their thinking on what is to be done to learn what the cardiac defect is, how best to correct it, and also when correction is to be done in those infants who are not any more than 1 year of age.

Dr. Potts:

In the simplest congenital cardiac anomaly, namely patent ductus arteriosus, we find that a lot of children below 1 year of age require operation. We used to wait until the child was 2 years old, but by that time many of these children have large hearts, and some of them are even in failure. We have, in fact, found that in some of the more serious cases, operation is necessary even at 2 months. An additional number require operation at 6, 8, or 10 months of age. If operation is necessary, there is no reason why one should wait, since the 3 or 4 month old infant will tolerate surgery well.

Children with the tetralogy of Fallot are operated upon in the early days of life only if it is really necessary. We have performed surgery on approximately 100 children below a year of age with the tetralogy of Fallot. The operation is done only if the child is so blue that he is doing poorly (having attacks of syncope, for example), and obviously cannot continue to live without surgery.

Many infants with tricuspid atresia are in difficulty soon after birth and we have operated on this lesion a number of times in the first month of life. It is not possible to do much for many infants with tricuspid atresia; some of them make wonderful recoveries, many of them do not, but each is entitled to his chance to live.

Proceedings of the Weekly Pediatric Conference, March 28, 1958.
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‡ Cardiologist, Children's Hospital, Washington, D. C.

In the matter of interventricular septal defects, it has been recently commented that more than 95 per cent of all patients born with ventricular septal defects in the days prior to corrective surgery died prematurely, and further, that the mortality rate was particularly high during the first year of life. I do not agree with that statement and would like Dr. Nadas to comment.

Dr. Nadas:

We have recently reviewed 98 cases of interventricular septal defects studied at the Children's Hospital in Boston during a five year period, and of those 98 cases, we have lost only three. One child died on the operating table during an exploration to make a differential diagnosis between a patent ductus arteriosus and a ventricular septal defect with aortic regurgitation. A second one died during cardiac catheterization, and the third one died at another hospital. At the same time we investigated the records of the pathology department and found another three children with pure interventricular septal defects who died during the same five year period of time. This would mean to me that although an interventricular defect is a severe lesion, in most children, intelligent and vigorous medical management will enable the overwhelming majority to reach an age when they can be operated upon with a better risk.

Dr. Potts:

I agree. Often we have seen one of these young infants with enlargement of the heart and even heart failure, but with good medical management, in two to three years the heart may be normal in size and the child appear perfectly normal. He still has the defect, of course, but it is difficult to say if and when he needs an operation.

Dr. Nadas:

Another point frequently mentioned is that even if these children do not die, they are doomed to develop fulminating vascular disease. In other words, they may live, but the price they pay for survival is irreversible change in the pulmonary vascular resistance. This is possible, but we have restudied 25 patients with interventricular septal defects by cardiac catheterization after a four year or more interval. We found that in these 25 patients there has been no increase in the pulmonary vascular resistance.

This does not happen all the time. There will be some patients, even in the pediatric age group, I suspect, in whom it will progress. In most however, the resistance will not progress until the late teens, twenties or thirties. In some instances, the pressure has even come down. This has happened because these infants have gotten over their pneumonias and started breathing better.

Dr. Walsh:

Dr. Nadas, how would you manage a patient a few weeks to 2 or 3 months of age who has a loud, long, systolic murmur maximal along the mid portion of the left sternal border, hypervascular lung fields, a well split P-2, whose electrocardiogram shows either a left ventricular or biventricular hypertrophy pattern, and who is in congestive heart failure, and following proper medical management, responds slowly, but stays in a borderline failure?

Dr. Nadas:

On the basis of our series of cases in these past few years, a baby who is not overtly cyanotic, but who has evidences of a sizable left to right shunt with congestive heart failure, should be investigated for a patent ductus arteriosus; that is the only one of this group of congenital heart disease with left to right shunt that we would feel inclined to operate on at that age group. However, in young infants who have interventricular septal defects and intractible cardiac failure, Dr. Gross has banded the pulmonary artery in 4 cases and in so doing, has placed the load on the right ventricle without exposing the pulmonary artery to the tremendous flow that a large ventricular septal defect entails. Two of these patients have died, the other two are doing well. Whether they would have done well without the banding procedure, I do not know, but these were babies who were in continual pulmonary edema for a matter of months despite vigorous medical measures. I would consider this operation as an emergency palliative procedure in such cases.

Dr. Potts:

We have not done any of these pulmonary banding procedures for interventricular septal defects. In the case of an infant with an atypical patent ductus that throws him into heart failure in the early months of life, when the diagnosis is made the infant is first digitalized, and as soon as adequate diuresis takes place, there is no choice but to operate on him. The ductus in these cases is often the size of the aorta. This is what we have done and with spectacular results. These children improve like magic after the ductus is closed.

We have operated on no child with tetralogy of Fallot using a pump oxygenator. I hope to dispel the idea that the reason we have not is because the alternative procedure carries my name. After all, operations come and go year after year. And indubitably, in time, a shunt operation will disappear. But at this time, I would prefer not to perform an operation with an operative mortality of around 30 to 40 per cent. Two institutions report a mortality somewhat lower, but last fall, in a meeting of the American College of Surgeons, I investigated the results compiled by eight of the

large cardiology centers. Of a total of 159 patients with tetralogy of Fallot who have been operated upon at these institutions, 56 had died; this is a considerable mortality. Of the ones who survived, these can be called cured only when 5 to 10 years have gone by. I am not criticizing open-heart surgery for repair of the tetralogy of Fallot, but our attitude today is this: we perform a shunting operation, whether subclavian-pulmonary or aortic-pulmonary, on those children who cannot get along without surgical relief. Those who can wait are waiting, and we hope that these lusty pioneers persevere and beat their way to good arable land.

The shunt operation is basically no good; it is a makeshift operation. All we are doing is shunting some blood to the lungs and leaving uncured all of the defects in the heart. We are also adding a strain to the child's heart. What is happening to these children we have operated on? The first half dozen we, of course, follow with great interest because of the emotional attachment, so to speak. The first child, who was operated upon at age 21 months, in 1946, is now 14 years of age, a young woman, hale and hearty. Her heart enlarged a little after the operation but the cardiac-thoracic ratio has since remained the same, and she is enjoying life. How long is she going to continue to enjoy life? I do not know. A second child, a cute little girl who was 4, who was so blue she could not get off her chair, was operated upon in November, 1946, and is now a blossoming young woman who does extremely well with a minimally enlarged heart. A third child we have operated on has a huge heart and is presumably going to die sometime in the next three to six years. We are currently performing a study of the first 50 children who were operated on more than 10 years ago to see what has happened to them, how many have died, and of what. This is also the sort of thing that has to be done with the pump-oxygenator cases.*

Dr. Nadas:

Dr. Potts likes his own child, as he says, which is perfectly natural; most living beings like their own children. Dr. Gross also loves Dr. Potts' operation and it is the one he prefers to use. The indications for operating on the tetralogy of Fallot in Boston are the same as they are in Chicago. The children have to be youngsters who are too sick to lead a happy life.

* On March 12, 1959, Dr. Potts added the following comments:

"Approximately a year has passed since our meeting in Washington and during this time the mortality, as was anticipated, has dropped considerably for the open heart correction of tetralogy of Fallot. I still am inclined to believe that we have no choice but to do a shunt operation on the ill, cyanotic infants with tiny pulmonary arteries. Older children, I feel sure should have intracardiac surgery.

"Incidentally, since making this report a year ago we have operated upon ten tetralogies with the aid of extracorporeal circulation. I must add that good fortune has smiled upon us because there has been no mortality in these ten cases."

This is a broad statement and may involve a 5 year old who cannot play with the other children, or it may involve a small baby who cannot live without oxygen. I think that when you begin using the pump oxygenator, you first ought to do the easier, simpler operations and lead up to a repair of the tetralogy, which, as Dr. Potts described, is a formidable technical challenge. So that up until January or February of this year, we have not operated on any patient except one who badly needed it, and in those we have operated on, we have done a shunt. In February, after we felt reasonably secure about repairing atrial septal defects, pure pulmonary stenoses, and interventricular septal defects by open methods, we started operating on the tetralogies. The first three died; in two of these we had no choice, since they were people who had had a previous shunting operation. The third had very marked cyanosis. The next two were much less cyanotic than the first three and had oxygen saturation values in the range of 80 to 85 per cent. Both survived and did well; they have no murmurs and are pink, but I do not know what their oxygen saturation is now.*

Dr. Walsh:

When do you think coarctations of the aorta should be repaired? Have you done a repair under 3 years of age?

Dr. Potts:

If we have a choice, we prefer to repair a coarctation between 7 and 9 years of age. We have operated on approximately a hundred patients and we have had two deaths, both in little children. Although some would disagree, I have a feeling that little children with a coarctation who are 1, 2, or 3 years of age rarely need an operation for the adult type of coarctation.

Dr. Nadas:

We feel that babies with coarctation of the aorta who are discovered to have the coarctation accidentally need nothing done until they are older. Infants with coarctation of the aorta who have large hearts and are in cardiac failure, we think can be treated medically. If they do not respond

* On July 27, 1959, Dr. Nadas added the following:

"Since March of 1958 we in Boston also had much better luck with open heart surgery on the tetralogy of Fallot syndrome; as a matter of fact the first 6 consecutive cases all survived with complete repair. On the basis of our present experience, we would recommend that a shunt operation—preferably a Blalock procedure—be done on all infants who are badly in need of surgery. Children weighing 25-30 pounds or more should have complete correction of their tetralogy of Fallot complex, and the operation postponed to the time where symtomatology is appreciable—but probably not beyond puberty."

to medical treatment, then the chances are that we are dealing with a coarctation complicated by another lesion. We have operated on 3 patients with coarctation of the aorta in the infant age group; two of them are dead, one is somewhat improved. I would like to join Dr. Potts in saying that babies with coarctation of the aorta ought to be treated vigorously by medical means if necessary, but left alone if they are not in difficulty. If medical means do not result in improvement, we then attempt operation, but realize the much higher risk.

Dr. Walsh:

In our time, as we all know, there are new and better medical gadgets, and better recording devices, all of which are very expensive. I would like to hear your comments on what your concept is of the practical use of auxiliary aids, namely cardiac catheterization and angiocardiography, in the diagnosis of anatomic defects of the heart.

Dr. Nadas:

Obviously, these research instruments represent tremendous advances and they have their place on the cardiovascular service. I do not think it is possible to do cardiac research nowadays without them. In the diagnosis of these congenital cardiac lesions, I think Dr. Potts and I agree that probably somewhere around 75 per cent can be diagnosed by an intelligent cardiologist using the conventional tools of stethoscope, x-ray, and electrocardiography. An intelligent use of cardiac catheterization techniques, including good oxygen analyses and good pressure measurements, would probably add another 10 per cent.

Dr. Potts:

If I may be allowed a few moments of philosophical discussion, I would like to say that I grew up under the teaching of Dr. Stanley Gibson. Dr. Gibson was one of the greatest of the great cardiologists of this country. He learned his cardiology before any operation had been done. When surgery was first introduced, he could tell you an unbelievable amount about a child's heart simply by placing a stethoscope on the child's chest. I am sure I lean over backward in my attitude toward the simple methods of diagnosis. I plead again for the listening to thousands and thousands of hearts until each murmur begins to take on its significance. When we arrive at this point, many poor unfortunate children will not be put in bed for four to six months because of a hemic murmur.

Dr. Nadas:

Let us, however, not lose sight of the fact that our heart auscultation is a great deal better today because of the fancy gadgets. In the 1945–46

edition of Dr. Helen Taussig's book, she said she had never seen a case of isolated pulmonary stenosis. The reason why I am sure she had seen them but had not recognized them was that she did not have the aid of the fancy instruments like the heart catheter which help us to recognize what the murmur of pulmonary stenosis is. It is simple once you know it, but the pulmonary stenosis murmur was formerly classified as evidence of a ventricular septal defect 75 per cent of the time. I think we have learned a great deal from the heart catheter and the angiocardiograms and are learning all the time; once we have learned it, we translate it into plain ordinary clinical language.

Dr. Walsh:

With the development of definitive surgery for the treatment of atrial septal defects, do you think that ostium secundum defects should be closed routinely, or are you operating on just some within that category?

Dr. Potts:

For a while, we closed ostium secundum defects by various and sundry closed methods which we have since stopped using. Which auricular defects should be closed? So far we have done only those that we were sure needed to be closed; these would include those defects with a large shunt resulting in a large heart. Our method now differs from that of Dr. Gross. For the last several years we have been closing all interatrial defects under hypothermia which we have found very satisfactory.

Dr. Nadas:

We feel that all atrial defects with a sizable shunt should be closed. What is a sizable shunt? If catheterization data are available, I would say a large shunt produces at least a two to one ratio between pulmonary and systemic flow. If catheterization data are not available, I think a large heart, hilar dance, and apical diastolic rumble are sufficient indications. We are closing these atrial defects by open-heart surgery like Dr. Potts, but are not using hypothermia; we use the pump oxygenator instead.

Congenital Toxoplasmosis

Discussion by: LEON JACOBS, PH.D.*
Case report by: DONALD W. WICZER, M.D.†

Congenital toxoplasmosis is an increasingly well recognized entity. This report presents a typical example of toxoplasmosis occurring in the newborn period and summarizes the positive clinical and laboratory aspects of this disease as well as the most recent hypothesis of the pathogenesis of *Toxoplasma* infection.

CASE REPORT

This 3 month old white female infant‡ was admitted to Children's Hospital on May 13, 1957. She had been referred from the American Hospital in Paris where one week earlier her illness was diagnosed as congenital toxoplasmosis. Abnormality was first noted by the parents one month prior to admission when she was found unable to follow objects with her eyes or react to light. During a routine physical examination eight days before admission there was evidence of hydrocephalus. Further examination showed a pigmented plaque of chorioretinitis located in the macular region of the left eye; the right eye showed a synechial iris lesion, iritis, cloudy vitreous and a gray colored lesion of undetermined size located on the temporal side of the optic disc.

The infant was born five weeks prior to the expected date of confinement and weighed 4 pounds 3 ounces. After a normal delivery she was placed in an incubator with oxygen at a concentration of less than 30 per cent for 24 hours. On the second day of life jaundice was noted. A Coombs's test was performed and was negative. There were no other physical abnormalities noted at birth. The placenta was described as normal.

The mother was living and well, but a positive history of toxoplasmosis was known to exist. No further information was available pertaining to this. The father was well, and there was one older sibling in good health.

Fluid obtained from the right and left lateral ventricles contained 100 mg. and 240 mg. of protein per 100 ml. respectively. Bacterial cultures of fluid from both ventricles were negative. Lumbar puncture after injection of methylene blue into the ventricle was traumatic and no dye was detected. Toxoplasma dye test titers were reported as 1:500 in the blood serum and 1:10 in the ventricular fluid.

The infant was then sent from Paris to the Children's Hospital for neurosurgical treatment. At the time of her admission there was no complaint of convulsions, drowsiness or lethargy. She ate and slept well. She was a well developed and well nourished white baby who appeared to be in no distress. Her head was 17½ inches and her chest 15¾ inches in circumference. Her temperature, pulse, and respirations were normal. Her weight was 13 pounds 4 ounces. Her head appeared slightly increased in size and had a prominent venous pattern over the parietal regions; there

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† Resident, Children's Hospital.
‡ Private patient of Dr. James W. Watts, Attending Staff, Children's Hospital.

was a suboccipital erythematous rash which blanched with pressure. The fontanels were open and the anterior fontanel bulged slightly. The sutures were open and the sagittal and parietal sutures were separated about two centimeters. The pupils reacted to light. There was evidence of chorioretinitis in the left eye. The Moro reflex was absent. The remainder of the physical examination was normal.

Complete blood count and urinalysis on admission were normal except for a hemoglobin of 9.8 Gm. per 100 ml. Two days after admission, subdural and ventricular taps were done together with a ventriculogram. The right subdural fluid contained 330 mg. of protein and 31 mg. of sugar per 100 ml. and no cells. The left subdural fluid contained five cells per cu. mm., all lymphocytes, 375 mg. of protein per 100 ml., and 31 mg. of sugar per 100 ml. Ventricular fluid contained 89 cells per cu. mm., of which 90 per cent were lymphocytes, and 930 mg. of protein per 100 ml. Roentgenographic examination of the skull in the anterior-posterior and lateral views revealed the calvarium to be enlarged. The anterior fontanel was widely patent. There were a few calcific deposits in the left suprasellar area. The appearance was described as that of hydrocephalus with intracranial calcification.

Nine days after admission a suboccipital craniectomy was performed, and after an obstruction in the aqueduct of Sylvius was discovered, a Torkeldsen's procedure was carried out. The child's temperature was elevated to 103°F. for five days following surgery, but was normal thereafter. Ten days following admission the infant's serum had a toxoplasma dye test titer of 1:8,000 and the mother's serum a titer of 1:32,000. Serum was injected intracerebrally and intraperitoneally into white mice, but no parasites were recovered. The child was treated with sulfisoxazole and chloramphenicol postoperatively. Arrangements were made for the child to be institutionalized and this was carried out following discharge from the hospital. At the time of discharge one month following admission, her weight was 13 pounds 4 ounces, and her condition was satisfactory but deteriorating. Death occurred five months later in another institution.

DISCUSSION

Toxoplasma gondii is a very small intracellular parasite. It is capable of invading a wide variety of cells; unlike many viruses it lacks specific cellular tropism. It has been found in many types of cells, for example, liver parenchymal cells, lung alveolar cells, cells of the central nervous system (both neurones and glial cells), renal tubular cells, and in heart and skeletal muscle, to name but a few. The parasite is widely distributed among the animal kingdom. It is a crescent-shaped organism, 3 x 6 microns in size and refractile under the microscope. It has a somewhat eccentric nucleus and a small glycogen granule closer to one end. It has a very complicated structure and contains a variety of organelles not thus far described in other groups of protozoa. Its mode of reproduction is such that we can not classify it with other organisms which it superficially resembles, such as the malaria parasite, because it divides only by longitudinal fission, so far as we know, while the malaria parasite goes through schizogonic cycles. There are a few organisms found in other animals which resemble it a little, and possibly these will make up another group of protozoan organisms. In tissue culture, as a result of a large number of protozoan

divisions, the host cell is often completely filled with toxoplasma organisms. Interestingly enough, the host cell may undergo a mitotic division despite the presence of the parasite. In the brain or eye, or in muscle, there may also be encysted parasites which have a different appearance from the free parasites in that they have a little larger glycogen vacuole and are thinner; these cysts are somewhat more resistant to the external environment.

In the acute stage of the infection when the parasite is first introduced into the body, there is characteristically a local proliferation at the site of entry and then dissemination through the blood stream to many organs. This stage in experimental animals lasts about one or two weeks, and in those organs which the parasite penetrates, there are focal areas of necrosis resulting from the intracellular proliferation of the parasite and the rupture of infected cells. After this stage, the antibody response becomes evident, the parasitemia clears, and there is a gradual diminution in the number of parasites in the liver, spleen, and lungs until they are no longer found. Nevertheless, a proliferation of parasites in the central nervous system continues, and this is the subacute stage of the infection. The chronic stage follows. In this stage, there are probably no longer any proliferating forms, but the parasite is found in cysts in the central nervous system and in muscle, but usually not in the viscera. There is some question as to the origin of the wall of these cystlike structures; it was formerly believed to be a residuum of the host-cell wall, or *pseudocyst*, but we are beginning to believe that it also represents a contribution from the parasite, in which case it would be a true *cyst*.

The characteristics of the disease, as it is seen in human beings, are related to the stage of infection. In the acute stage of the congenital infection, there is a visceral form of toxoplasmosis in which there is a variety of symptoms including vomiting, diarrhea, drowsiness, convulsions, leukocytosis, jaundice, splenomegaly and hepatomegaly, irregular fever, purpuric spots, or a maculopapular rash; there can be electrocardiographic changes consistent with a myocarditis, or a pneumonitis, or pleural effusion. The bulk of cases of congenital toxoplasmosis represent the subacute stage of infection, as in the infant presented today. In this stage there is little or no fever, and the symptoms are predominantly those referrable to the central nervous system. There may be hydrocephalus, chorioretinitis, and cerebral calcifications. Chorioretinitis occurs in 80 to 90 per cent of cases, hydrocephalus in 50 to 60 percent, and cerebral calcifications in 30 to 40 per cent. These calcifications are diffusely distributed and show no localization to the ventricles or choroid plexus as is found in certain other diseases.

When this infant died, some five months after she had been discharged from Children's Hospital, we were able, by injecting mice, to isolate

parasites from her brain. eye, heart, skeletal muscle, and from several other organs. But while we were able to isolate these parasites by animal techniques, we could not find them in histopathological sections even after a long search. It is difficult to decide whether the parasites were in the proliferating form or the cyst form, but the fact that they survived various digestion techniques used to concentrate large amounts of tissue suggests that they were in the cyst form. When tested for its virulence in other laboratory animals, this particular parasite was found to be an extremely mild strain which was not capable of doing much damage. The crux of this infant's difficulty was the occurrence of the infection around the aqueduct of Sylvius, with destruction of the ependyma, and fibrotic proliferation which occluded the aqueduct lumen so that internal hydrocephalus developed. In the chronic stage of the infection other symptoms due to *Toxoplasma* occur. Sometimes a child is born without any symptoms and remains asymptomatic during the first year of life, but later on develops a chorioretinitis as the only evidence of congenital toxoplasmosis. In adults too, we are quite convinced that chorioretinitis is frequently due to toxoplasmosis.

The acquired form of the disease also sometimes occurs in children. There have been a few cases of encephalitis which have been shown to be due to *Toxoplasma*; in these cases there are no symptoms referrable to any other organ. A more severe form of the disease, a rickettsial-like syndrome with pneumonitis, encephalomyelitis, maculopapular rash and fever, has been found in adults but not in children. The lymphadenopathic type which occurs in both children and adults resembles infectious mononucleosis; there is a remittent fever, some lymphadenopathy, lethargy, malaise, and great fatigue. Myocarditis is attributed to *Toxoplasma* by some workers and *Toxoplasma* has been isolated from the heart in one instance, but much investigation must be done to determine how frequently this occurs.

The dye test of Sabin and Feldman is used to make a specific diagnosis of toxoplasmosis. Live parasites from infected mice are incubated with the suspected serum and an accessory factor (which is present in normal human serum and which seems to be composed of complement and the properdin substance of Pillemer). After incubation the organisms are exposed to alkaline methylene blue. If the toxoplasma organisms appear somewhat rounded and intensely blue colored, the test is negative and the serum contains no antibody. On the other hand, if after exposure to antibody-containing serum the organisms become distorted and are very pale because they have not taken up any dye, antibody is present and the test is positive. This is the basis for practically all of the diagnostic testing now done on *Toxoplasma* because the complement-fixation test is not as valuable a test. Unfortunately the dye test is such a difficult one that very few laboratories

perform it. It is unlikely, because of the risk of working with these organisms, that it will ever be used as a routine test in hospital laboratories; for that reason we at the National Institutes of Health are trying to develop another test.

The dye test is the earliest of the serologic tests for toxoplasmosis to become positive; it reaches high titers, and remains positive for a long time. The complement-fixation test becomes positive sometime after the dye test, reaches relatively low titers, and becomes negative earlier. The one advantage of the complement-fixation test in the diagnosis of some cases of congenital toxoplasmosis is that if the dye test has already become positive and has reached a stable high titer, a rise in titer of the complement-fixation test or a shift from negative to positive can be indicative of active or early infection. Many infants shortly after birth and early in the course of the infection show low titers of passively transferred antibodies; the mother's dye test titer is usually low also, and under these circumstances we certainly are not dealing with toxoplasmosis. Cases where the dye test titer in the infant is equal to, or higher than, that of the mother, and the complement-fixation test is positive and rising are consistent with a diagnosis of congenital toxoplasmosis. If a very young infant has a dye test titer higher than that of the mother and a negative complement-fixation test, this is consistent with an early recent infection regardless of whether or not the complement-fixation is positive or negative in the mother.

In our laboratory we have been working on a hemagglutination test which we hope will be generally useful. This test has compared quite well with the dye test in the case of serum specimens obtained in population surveys which only rarely included individuals with active infection. Our purpose was to reveal the experience of the general population referable to exposure to *Toxoplasma*; therefore the titers, as was to be expected, were stable. In the acute stage of the infection, however, we still have to determine how the hemagglutination test compares with the dye test in regard to rapidity of appearance and height as well as duration of titer.

Surveys of the general population show that there is an increase in incidence of positive serological reactions to *Toxoplasma* with increasing age. In a survey of the Washington Negro population, there is a surprisingly high percentage of positive tests in children under 9 years of age. In other series performed by other workers the percentage of positive reactions in this early age group is much lower, whereas it has been shown that in people over 50 years old, more than 50 per cent of the population has demonstrable titers. Geographically, there are considerable differences in the prevalence of antibodies to *Toxoplasma*. In the northern regions there is a lower rate than in the southern regions; the highest prevalence rates have been reported from places like Trinidad, the coastal areas of

the Caribbean, Tahiti, and from the island of Truk, while the lowest rates have been reported from Alaska, Iceland, and northern Sweden. Thus there may be some climatic factor involved in the transmission of toxoplasmosis.

The question arises whether the cyst stage of *Toxoplasma* is involved in the chronic form of the infection or whether it is important only in transmission of the parasite. The subacute and chronic forms of the infection seem sometimes to be due to hypersensitivity of tissues previously exposed to this parasite and to a severe inflammatory reaction resulting from the occasional escape of parasites enclosed within a cell into the sensitized tissue. The next question is whether these forms that do break out of cells were encysted or whether the parasites were merely proliferative forms which were lying dormant within a host-cell wall without ever having gone on to form the encysted stage. In the ocular form of the disease both continuing lesions which never cease to be active and lesions which flare up and subside spontaneously are seen. We believe these are due to two different pathogenetic mechanisms. On the one hand, continued proliferation of the organism behind the blood-brain or blood-ocular barrier over a long time, in spite of antibody-production, is believed to cause continuing lesions. On the other hand, lesions which flare up and subside are believed to be due to the escape of intracellular parasites which may have previously been encysted forms or dormant proliferative forms. Another pertinent point is that while early treatment using pyrimethamine and sulfadiazine will cure experimental infections in mice and other experimental animals, this result does not obtain in the subacute or chronic stage of the infection; in this stage the drugs fail to eliminate the organisms which can be detected by grinding up brain or muscle and inoculating these tissues into other animals. Therefore, treatment of congenital toxoplasmosis should be expected to be successful only in the acute visceral form of the infection, and to be unsuccessful in the subacute or chronic stage. There is one exception: Chronic toxoplasmosis of the eye can definitely be due to proliferative forms, and in these cases drug therapy is helpful.

How is infection with *Toxoplasma* acquired? The proliferative stage of the organism is very sensitive to the external environment, and even in serum or well balanced media in the laboratory it will not survive more than 24 hours. The organism can not stand heating or even slight changes in osmotic pressure. The question arose, as in the case of other protozoa, whether transmission could be effected by an arthropod such as the mosquito or the tick; we have not been successful in proving this. More recently we have turned our attention to the cystlike stage which we have found is much more resistant to the external environment. This stage survives heating and digestion somewhat better, and changes in osmotic pressure

considerably better. So we now believe that human beings possibly acquire the infection by the ingestion of infected flesh. Cysts in the muscle of rats occur rather frequently. When we did surveys of pork muscle, we found 12 positives from 50 samples, detected either serologically or by isolation of the organism or both. Of 60 beef specimens, none has been positive, but serological studies of cattle have shown that the distribution in these animals is spotty, i.e., one farm may have infected animals and another not. We have recently found toxoplasmosis in sheep, in which we had 10 positive out of 80. These findings are consistent with those of Georges Desmonts in France who has noted that there are some orphan homes in Paris where it is a practice to feed the children raw meat after the first year of life, and this is when the positive dye test titers begin to appear in these children. On the basis of our present knowledge, the ingestion of raw meat should be avoided by pregnant women. This is not the only factor involved, however, because a survey of serum from Seventh Day Adventists who had not eaten meat for 20 or 30 years showed some individuals with high serological titers. Either *Toxoplasma* occurs in other foods of animal origin, such as milk and eggs, or there is another method of transmission.

Feldman and Eichenwald, who have done the bulk of the studies in this country on congenital cases and follow-ups, feel that mothers who have delivered an infant who has congenital toxoplasmosis have just as good a chance as any other woman in the general population of having a normal delivery next time. There is, however, always a possibility that a woman could give birth to more than one affected child. Originally, various workers in Europe made some conjectures about this, but there is no clinical or laboratory evidence to support what they have to say in regard to *human* infection. However, they also have done experimental work in rats where it was very definitely established that congenital transmission from chronically infected rats to offspring occurred with greater frequency than one would expect. We have just finished a large study of chronic *Toxoplasma* infection in rats and have had only one case of definite congenital transmission from a chronically infected rat to a few offspring in one litter. The interesting thing is that on two occasions we have found *Toxoplasma* in the uterus of these rats. The Germans have assumed that there is a parasitemia during pregnancy. We have never been able to prove this, but if we concede the idea of the parasites residing within the uterus and the placenta growing out near the parasite-containing areas, we can see a possible route of congenital transmission in a mother with a chronic infection, in the absence of a generalized exacerbation. We next decided to extend this study to uteri of women who die of other causes and the very first uterus we picked up had encysted *Toxoplasma* in it. This woman had died of a myocardial infarction and had no history of any acute disease resembling toxoplasmosis.

It is now conceivable that a case of toxoplasmosis which is very mild in the child may nevertheless be congenital. Such a case which appears long after birth may be due to the fact that at the same time the parasites are transmitted antibodies and complement are also; then after the passively transferred antibodies diminish, activity of the parasites results in much milder symptoms than occur in the general run of cases that have been described. We are not yet certain as to the frequency with which this might happen, if indeed it does, but it is a problem for continued study.

Lead Encephalopathy in Infants and Children

WELLINGTON HUNG, M.D.*

Lead encephalopathy has been recognized as a clinical entity for over a century. According to Aub, Fairhall, Minot and Reznikoff[1] the nervous manifestations of lead poisoning were first described by Discorides. Tanquerel des Planches, in 1839, is credited with describing the clinical picture of lead encephalitis.[2]

An infant or child with lead poisoning is considered to have encephalopathy if he shows one or more of the following manifestations: convulsions, lethargy, coma, irritability, personality change, persistent vomiting, cranial nerve palsies, muscle weakness or paralysis, signs of increased intracranial pressure, and an increased protein concentration with or without pleocytosis in the cerebrospinal fluid.

The occurrence of lead encephalopathy is almost entirely restricted to infancy and childhood. Jacobziner and Raybin[3] have stated that approximately 50 per cent of all infants and children with lead poisoning have encephalopathy. Chisolm and Harrison[4] have suggested that the more frequent occurrence of encephalopathy in children as compared with adults may depend in part upon their more intense exposure rather than upon any inherent biological difference between children and adults. The greatest incidence occurs between one year and three and one-half years of age.[4, 5] Lead encephalopathy is seen most frequently in the lower economic strata.[3, 6]

There is a definite seasonal variation associated with the onset of this process which appears mainly in the summer months.[7] Chisolm and Harrison[4] have indicated that after a minimum of three months of daily

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exposure to lead as a result of continued pica, the advent of summer is the controlling environmental factor in the precipitation of acute lead encephalopathy. Although the mechanism of this phenomenon is not fully understood, Rapoport and Rubin[7] have presented experimental evidence in animals which indicates that vitamin D and the ultraviolet radiation of the summer sun increase the absorption of lead from the intestinal tract. Blackman[8] has suggested that the increased heat of summer leads to dehydration and acidosis in small children and that this factor may play a role in the production of lead encephalopathy. Byers and Maloof[9] have emphasized that lead remains stored in the skeletal system and that metabolic stress, such as fever, acidosis, or alkalosis may stimulate the release of this lead from the bones and thus precipitate an episode of acute lead encephalopathy.

CASE REPORT

S. W., a 19 month old Negro girl was admitted to Children's Hospital July 4, 1958 because of a sudden onset of lethargy and vomiting of one and one-half days' duration. There were five vomiting episodes associated with meals on the day prior to admission. There were two further vomiting episodes on the day of admission. There was a history of pica of three months' duration, the patient having chewed on the window sills and doors around her home. There was no history of convulsions, coma, restlessness, or mental or physical retardation.

Past history and family history were noncontributory.

On physical examination this Negro girl appeared well developed and well nourished but moderately lethargic. Her rectal temperature was 100.6°F., pulse 110, and respirations 38. Her head was symmetrical and the fontanels and sutures were closed. The pupils were round, regular, and equal, and reacted to light and accommodation. Funduscopic examination revealed no abnormalities. The ears, nose, and pharynx were normal. The lungs and heart were clear. There were no masses, scars, or tenderness of the abdomen. The skin was clear. Neurological examination revealed all the cranial nerves to be intact. The deep tendon and superficial reflexes were equal and active bilaterally.

Admission urine was acid, contained a trace of albumin, 3 plus sugar, and was slightly positive for acetone. There were 3 to 7 white cells and 2 to 3 red blood cells per high power field. The admission white blood count was 30,000 with 70 per cent segmented forms, 22 per cent lymphocytes, 1 per cent eosinophils and 6 per cent monocytes; blood hemoglobin was 7.6 Gm. per 100 ml. and hematocrit 35 per cent. The reticulocyte count was 5.1 per cent. Basophilic stippling was present. The cerebrospinal fluid was clear and contained 44 cells, 96 per cent of which were lymphocytes and 4 per cent polymorphonuclear cells. Sugar content was 76.5 mg. per 100 ml. and protein content 40 mg. per 100 ml.

Three days after admission, the blood urea nitrogen was 7.5 mg. per 100 ml., serum chlorides 104.7 mEq. per liter, carbon dioxide combining power 22.3 mEq. per liter, serum sodium 135 mEq. per liter, and serum potassium 4.2 mEq. per liter. The blood lead level was 0.41 mg. per 100 ml., the urine lead content 11.80 mg. per liter and the lead content per 24 hour specimen of urine, 4.01 mg.

X-ray examination of the skull showed some condensation of the inner table particularly in the frontal region consistent with chronic lead poisoning. X-ray exami-

nation of the long bones of the upper and lower extremities showed transverse lines of increased density in the metaphyses consistent with chronic lead poisoning.

On admission to the hospital intravenous fluids were started. Blood was drawn for a blood lead level and the collection of a 24 hour specimen of urine was begun. Following this the patient was given the calcium disodium salt of ethylenediamine tetracetic acid (EDTA) by clysis every eight hours. Later the child was markedly irritable but a neurological examination was normal. On the third hospital day she had a generalized convulsion lasting approximately 10 minutes which responded slowly to 2 grains of sodium phenobarbital given intravenously over a 20 minute period. During the physical examination at this time the pupils were noted to react sluggishly to light. The deep tendon reflexes reacted normally and were equal bilaterally. There were no pathological reflexes present. Approximately one and one-half hours after the first convulsion a second generalized convulsion occurred and lasted approximately two minutes. The patient expired suddenly on the third hospital day.

At autopsy, the brain filled the cranial cavity and was tense beneath the dura. Its consistency was soft and friable, making satisfactory removal from the cranium impossible. No exudate was seen over the surface. The cranial nerves appeared to be grossly normal. The gyri were flattened and the sulci obscured. The blood vessels forming the circle of Willis appeared normal. After fixation the brain appeared symmetrical. The sulci were slightly narrowed. The striking feature of the brain was the considerable degree of pallor. The ventricles were small and symmetrical.

Microscopically the blood vessels did not appear congested. There was no evidence of petechial hemorrhage or other lesions. Histopathologically, there was perivascular edema. An occasional blood vessel showed proliferation of its endothelial lining, and a rare thrombosed arteriole was seen. There was no evidence of gliosis. The meninges showed no evidence of inflammation. The final pathological diagnoses were: 1) encephalopathy due to lead poisoning (edema and vascular degeneration), 2) cloudy swelling of the liver, and 3) bone marrow hyperplasia.

DISCUSSION

Etiology

The most common predisposing cause of lead encephalopathy in infants and children is their habit of chewing paint from cribs, toys, furniture and woodwork, and the eating of plaster and fallen paint flakes. The tendency to put things in the mouth, though normal in the first year of life, is considered to be abnormal if continued into the latter part of infancy, and is referred to as pica.[6, 10] Pica is the usual forerunner of lead encephalopathy.

Clinical Findings

The symptomatology of lead encephalopathy is not specific but is similar to that found in those conditions where increased intracranial pressure is found. Not infrequently, prodromal symptoms referable to the gastrointestinal tract occur first; these include anorexia, vomiting, constipation, and abdominal pain. Nonspecific central nervous system symptoms in the form of headaches, irritability, lethargy, or changes in personality may accompany the gastrointestinal symptoms. The symptoms referable to the

central nervous system are usually manifested later in the course of lead poisoning than those of the gastrointestinal tract.

Convulsions constitute the most characteristic feature of lead encephalopathy. The convulsions may assume a variety of forms. They are persistent and difficult to control even with large doses of sedatives. Coma may be present. Nuchal rigidity associated with Kernig's and Brudzinski's signs may occur. The reflexes may be either hyperactive or hypoactive.

The increased intracranial pressure that accompanies the encephalopathy may be manifested in the infant or young child by separation of the sutures or bulging of the anterior fontanel. There may be papilledema or retinal hemorrhages. Changes in the pulse, respiration, or blood pressure may occur with high intracranial pressures.

Laboratory Findings

Laboratory and roentgenographic examinations are often invaluable aids in diagnosis, but must be correlated with a history of pica. Roentgen examination of the long bones, as originally described by Park, Jackson and Kajdi,[11] are valuable aids in the diagnosis of lead poisoning. The characteristic finding is a band of increased density at the metaphyses of the long bones.

Hematologic study usually reveals a microcytic hypochromic anemia of moderate to severe degree frequently associated with basophilic stippling of the erythrocytes and a reticulocytosis. Urine examination frequently shows slight to moderate albuminuria and acetonuria with granular casts in the sediment. A positive Benedict's test may also be present as a result of renal glycosuria due to a toxic effect of lead on the renal tubules.

A valuable presumptive laboratory test is the determination of urine coproporphyrins which are increased in lead poisoning. An increased urine excretion of coproporphyrins is not pathognomic of lead poisoning, but most children with lead poisoning do show an abnormal degree of coproporphyrinuria.

In lead encephalopathy the cerebrospinal fluid usually shows an increased concentration of protein; pleocytosis is less often found. The fluid is clear but is usually under increased pressure.

The most specific diagnostic test is the determination of the blood lead concentration. The generally accepted range of normal lead content of the blood is less than 0.06 mg. per 100 ml. of blood, but levels between 0.03 and 0.06 mg. per 100 ml. of blood are presumptively abnormal. Urine lead excretion can also be measured, and if it is increased above the normal range of 0.05 to 0.08 mg. per liter of urine per 24 hours, lead poisoning is present.

Diagnosis

Since it is difficult to obtain a rapid determination of the concentration of blood or urine lead, reliance on the physical findings of encephalopathy, a history of pica, and x-ray changes of the bones must be the basis of a presumptive diagnosis. A high index of suspicion is important.

The importance of early diagnosis also cannot be overstressed. If lead poisoning is discovered in its incipient stage, the child is treated promptly, and further exposure to lead is prevented, the end results are good. If, however, the diagnosis is not made until encephalopathy has developed both the mortality and morbidity rates are high.

Prognosis

The prognosis in lead encephalopathy, especially when convulsions have occurred, is grave. The mortality rate in lead encephalopathy has been reported in various series to be between 25 and 35 per cent.[3, 5, 12-14] Fatalities have been reported to be higher in the female.[5] No adequate explanation for this has been found. In 1956, there were 47 deaths reported throughout the United States for all ages due to accidental poisoning by lead and its compounds;[15] of these, 33 were of children under the age of 5 years. Those who survive the episodes of lead encephalopathy are apt to show some degree of permanent central nervous system damage. Jacobziner and Raybin[3] have stated that approximately 35 per cent of those who survive are left with permanent brain damage. This may take the form of recurrent convulsions, cerebral atrophy, tremors, muscular weakness, blindness, or speech defects.[6, 16, 17]

Pathology

In lead encephalopathy the brain is usually pale and edematous, and markedly increased in weight. There is flattening and pallor of the convolutions, and downward displacement of the medulla is common. Diffusely distributed punctate hemorrhages have been reported, dependent apparently upon changes in the arterioles, venules, or capillaries.[18] Blackman[8] found the brain to be permeated by a serous exudate which was so abundant in some areas as to cause the tissue to be distended and spongy. The capillary vessels showed thrombi in some cases.

Treatment

The treatment of infants and children with lead encephalopathy has been universally unsatisfactory. Despite the various forms of therapy employed over the years, the results obtained have been generally poor and inconsistent. Treatment is divided into three parts: 1) the control of convulsions, 2) the reduction of increased intracranial pressure, and 3) the

removal of lead from the body. The convulsions are difficult to control with the usual sedative drugs (such as intravenous phenobarbital), and may require general anesthesia.

In mild cases of encephalopathy it may be possible to control the increased intracranial pressure with frequent lumbar punctures.[19] In severe cases, these measures will be inadequate to reduce the increased intracranial pressure and surgical decompression may have to be carried out. McLaurin and Nichols[20] have advocated extensive bilateral decompression of the cranial vault to combat severe lead encephalopathy.

With the advent of BAL, some observers reported a lowering of the mortality rate of acute lead encephalopathy.[14, 21] In general, however, this agent was not completely satisfactory.

Since 1952, a promising new agent, the calcium disodium salt of ethylenediamine tetracetic acid (EDTA) has been used.[22-24] This drug is a chelating agent which, when administered during the acute phase of lead poisoning, causes a 25 to 50 fold increase in the output of lead in the urine. EDTA may be given intravenously, intramuscularly, or subcutaneously. Regardless of the route of administration, the total dose recommended is usually 75 mg. per Kg. of body weight per 24 hours, repeated daily for five days, followed by a rest period of three days and a second course for another five days.[19] The total daily dose is divided into two or three injections given at 8 or 12 hour intervals.

In 1952, Bessman, Ried, and Rubin[22] first reported the successful use of EDTA in lead encephalopathy in children. Bessman, Rubin, and Leikin[23] reported the successful treatment of 6 out of 7 children with lead encephalopathy with no toxicity from the drug; the child who died probably was treated insufficiently, having received only 0.5 Gm. of EDTA. The authors also presented evidence that EDTA allows lead to be removed from the patient even during the severe phase of encephalopathy without causing an exacerbation of the symptoms. Karpinski, Rieders, and Girsh[24] concluded that EDTA is highly effective in mobilizing lead *in vivo* and in causing rapid excretion of lead in urine. They reported there were no toxic signs accompanying the mobilization and excretion of lead by EDTA. Byers and Maloof[9] reported the use of EDTA in 3 children with lead encephalopathy and stated that "clinical evidence of plumbism rapidly clears."

Chisolm and Harrison[19] compared groups of patients with acute lead encephalopathy treated with EDTA and those treated with BAL. They found that while EDTA may have reduced the incidence of residual neurological damage to a certain extent, it has not significantly reduced mortality from this disease. They further suggest that EDTA was no more effective than BAL for quickly terminating coma, convulsions, and in-

creased intracranial pressure during an episode of acute lead encephalopathy.

Of special therapeutic importance is the control of infection and the resulting complicating acidosis which will tend to precipitate further attacks of encephalopathy by mobilizing lead from the storage depots. In the presence of encephalopathy and reduced renal function, corrective parenteral fluid should be administered with caution as the cerebral edema may be intensified.[19] Fluid administration should be merely sufficient to keep the patient from becoming dehydrated.

Some investigators[19] have advocated the use of repeated courses of EDTA during the convalescent phase following initial clinical recovery in an effort to prevent continuing lead toxicity to cerebral tissue.

Prevention of re-exposure to lead in patients who survive episodes of lead encephalopathy is of the utmost importance in helping to reduce severe permanent damage to the central nervous system. Lead encephalopathy is theoretically a preventable disease, and it is hoped that the increased attention being paid to this condition will result in its elimination.

SUMMARY

The clinical picture of acute lead encephalopathy is analogous to those conditions where increased intracranial pressure is found.

A case of acute lead encephalopathy in a 19 month child is presented, together with necropsy findings. Clinical and laboratory findings necessary to establish a presumptive diagnosis is presented.

A brief outline of the treatment of acute lead encephalopathy is given. The use of calcium EDTA is discussed.

The importance of early diagnosis of acute lead encephalopathy is stressed.

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The Editor's Column

Acres of Diamonds

In Russell Conwell's lecture,[1] "Acres of Diamonds," Ali Hafed sells a valuable farm to go forth in search of a diamond mine, little realizing that the property that he was giving up was to become one of the world's

greatest diamond mines. The moral of the story is that diamonds in the shape of opportunities are everywhere about us, if only we can recognize them.

How many young physicians who are about to begin their training in pediatrics appreciate the importance of exposing themselves to some postgraduate training in pathology? Thus far the American Board of Pediatrics has not recommended a definite period of training in pathology as a part of residency training in pediatrics, whereas the certifying boards of a number of the other specialties have been more specific in this regard.

The young physician may see more that attracts him on the ward than there is apparent in the seemingly quiet atmosphere of the clinical and pathological laboratories. It is significant that some residents in pathology require a period of readjustment and indoctrination before they can begin to appreciate and utilize the wealth of material about them.

Harvey Cushing,[2] in his biography of Sir William Osler, states that Osler "could hardly have realized until his later years that a long apprenticeship in the pathological laboratory always has been and always will be the only way to reach the very top for surgeon or physician." Osler's training as a morbid anatomist impressed upon him the necessity for making and recording careful and minute examinations of the patient. The examination begun on the ward was often not complete in his mind until he had visited the pathological laboratory.

How can one expect to have a complete understanding of congenital heart disease and the other developmental anomalies unless he sees and examines the various organs at autopsy and correlates these findings with those made during life? For the proper appreciation of the value of the clinical laboratory one should spend more than a few passing hours there if he is to gain the greatest help from it and also recognize its limitations. Sometimes a few minutes' examination of a blood smear by a trained observer may give the physician a more definite idea of the cause of his patient's disability than his observations on the ward. Only the microscopic examination of tissue can determine with certainty whether or not one is dealing with a cancer.

Consider the fine feeling of accomplishment which must have come to Osler when he recognized platelets in the blood for the first time, to Herrick when he first found sickle-cells in the blood, to Longcope who correlated the finding of atypical lymphocytes in the blood from patients with "glandular fever" with their clinical signs and symptoms, and to Hargraves who recognized the L. E. cell in lupus erythematosus. How satisfying must have been the putting together of the various clinical, biochemical and pathological findings to give us our present day understanding of cystic fibrosis of the pancreas. Both clinician and pathologist should be equally disturbed when they fail to recognize some important abnormality which

is subsequently perceived by another and more alert observer. The realization that many important findings await the alert and trained observer should be an ever-present stimulus for us to go forward. "Acres of diamonds" are all about us awaiting the cultivation of our powers of observation to find them.

E. C. R.

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Letter to the Editor

Operating Time IS Important!!!

Note is made of the "Editors Column" in the Clinical Proceedings of the Children's Hospital of March 1959 titled "Operating Time is Important." In the concluding paragraph it is stated that "safe deliberate speed in executing a surgical procedure is a prime factor in keeping down the morbidity and mortality in pediatric surgery."

Notation should also be made of the economics of "operating time" in all busy hospitals. In most hospitals charges for use of operating facilities and personnel are made on a unit of time basis. Unnecessary prolongation of "operating time" needlessly increases cost to patients. Whether charges are paid by insurance or directly "out of pocket," such cost is ultimately charged to the public.

The prompt attendance of physicians to their schedules, as well as in "the deliberate speed" of their surgery can definitely increase the work performed in a given period of time without increase of facilities or personnel.

Efficient use of facilities and personnel with consequent reduction of costs for hospital care wherever possible, is a responsibility of physicians as well as hospital directors.

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